Remarks

I. Status of Claims

Claims 14-27 were the subject of the office action dated September 5, 2008. The applicants hereby cancel, without prejudice, claims 16, 19, 20, and 25-26, in favor of the remaining claims. New claims 28-35 are added.

Thus, claims 14-15, 17-18, 21, 23-24, and 27-35 are now presented for further consideration.

Claims 15, 21, 22 and 23 are amended to put them into more proper dependent form.

Support for newly added claim 28 is found in the application as filed, for example, page 10, lines 31-33 of the specification. Support for claims 29 and 30 can be found in claim 14 and throughout the specification as filed. Claims 31-35 are variations of prior claims.

II. Claim rejections

A. Rejection under 35 U.S.C. § 112, Second paragraph; Indefiniteness

Claims 14-16, 24, 25, and 27 stand rejected as being indefinite.

The term "targeting sequences" is hereby removed without prejudice from claim 14; this should render this issue moot.

The word "essentially" is removed from claim 24 without prejudice; this should render this issue moot.

Claim 25 is canceled without prejudice in favor of claim 14. This should render moot the indefiniteness issue raised in the office action with respect to claim 25.

B. Rejection under 35 U.S.C. § 112, First paragraph; New Matter

Claims 14-27 stand rejected for introducing new matter. The applicants respectfully traverse the rejection.

The "optional targeting sequence" language is removed from claim 14 as being superfluous, as discussed above.

Claim 16 is canceled without prejudice, and this should render this rejection moot with respect to claim 16. However, paragraph 43 of the published specification is noted, which reads as follows:

> [0043] According to the invention, the protein HveC or nectin-1 and/or the immunoglobulin belong preferably to the homologous species.

See also paragraph 58, discussed below.

The remaining issues raised in this rejection appear to be that the specification lacks support for "the V domain or VCC domain of bovine nectin-1" and for bovine immunoglobulin. The applicants respectfully disagree. (This rejection should be rendered moot with respect to mouse immunoglobulin.)

Paragraph 156 of the published application (US 2006/0272040) refers to sequence 4, which is the VCC domain of pig HveC (also known as nectin-1) and the Fc fragment of porcine IgG. Paragraph 158 refers to the "pVCC" construct. Paragraph 159 refers to the "pV" construct and states that it used only the V domain of HveC (porcine). SEQ ID NO:3 sets forth a fusion protein comprising the V domain from porcine HveC fused with the Fc fragment of porcine IgG.

Various other sections of the specification make it clear that other equivalent parts can be substituted.

For example, paragraph 58 of the published application reads as follows [underlining added]:

> [0058] The invention also relates to a mammal belonging to a non-human species rendered resistant by germinal transgenesis to an infection by an alphaherpesvirus for which the polypeptide HveC or nectin-1 constitutes a functional receptor by the effect of the expression of a chimeric protein composed on the one hand of the extracellular domain of the nectin-1 or HveC or one of its parts preferably of the homologous species, and on the other of the crystallisable fragment of an immunoglobulin, particularly of a gamma type immunoglobulin preferably of the homologous species.

The term "preferably" makes it clear that *other* sources are also contemplated. Similar language is also in paragraph 39, as explained in a prior response, and in paragraph 43, above.

Paragraph 31 states (in relevant part, with underlining added):

> [0031] On the other hand, it has been demonstrated that the protein HveC, and particularly that of the pig, behaves like a functional receptor not only of the HSV-1 virus but also of the animal alphaherpesviruses PRV and BHV-1 (Milne, R. S. B., Connolly, S. A., Krummenacher, C., Eisenberg, R. J., and Cohen, G. H. (2001). Porcine HveC, a member of the highly conserved HveC/nectin 1 family, is a functional alphaherpesvirus receptor. Virology 281, 315-328; Cocchi, F., Menotti, L., Mirandola, P., Lopez, M., and Campadelli-Fiume, G. (1998)...

Milne *et al.* (2001), attached herewith, provides a sequence alignment between HveC proteins from six mammalian species including bovine. The sequence alignment in Milne illustrate a high degree of sequence identity between the V and the C domains of HveC proteins amongst various mammalian species. Milne further discloses specific amino acids residues that constitute the V, and the two C domains within the extracellular portion of HveC from various mammalian species.

Applicants also submit herewith the amino acid sequence alignments of the extracellular domains of the porcine and bovine HveC proteins. These sequence alignments further illustrate a high degree of sequence identity amongst porcine and bovine HveC protein. It is evident from the attached alignments and the Milne publication that a skilled artisan can recognize the conserved structural and functional domains of HveC amongst various mammalian species.

Paragraphs 36 and 47 of the published application state:

> [0036] It should furthermore be noted that the protein HveC has a remarkably well conserved polypeptide sequence between the mammal species; by way of example, 97% of the amino acids are common to the protein HveC expressed by the pig and the protein HveC expressed in cows, which implies a strong identity of structure and function in these two species.
>
> ...
>
> [0047] In all cases, only the part corresponding to the extracellular domain of this receptor will be used, or in another version of the process, a sub-part of this domain or even, where necessary, a polypeptide sequence essentially derived from this extracellular domain.

As explained in a prior response, paragraphs 60 and 61 teach that porcine and bovine sources can be used, and that PRV and BHV can be used:

> [0060] According to the invention, the alphaherpesvirus can advantageously be the PRV virus and the mammal belong to the porcine species.
>
> [0061] According to a variation of the invention, the alphaherpesvirus can also be the BHV-1 virus and the mammal belong to the bovine species.

Taken with paragraphs 156 and 159, it should thus be quite clear that the specification taught the use of bovine V/VCC in place of porcine V/VCC. All the foregoing should make it clear that the various specified domains can be used interchangeably according to the subject invention.

The same is true for the porcine or bovine immunoglobulin component. Again, paragraph 58 states (again with underlining added):

> [0058] The invention also relates to a mammal belonging to a non-human species rendered resistant by germinal transgenesis to an infection by an alphaherpesvirus for which the polypeptide HveC or nectin-1 constitutes a functional receptor by the effect of the expression of a chimeric protein composed on the one hand of the extracellular domain of the nectin-1 or HveC or one of its parts preferably of the homologous species, and on the other of the crystallisable fragment of an immunoglobulin, particularly of a gamma type immunoglobulin preferably of the homologous species.

In light of all the foregoing, the withdrawal of the rejections for new matter is respectfully requested.

C. Rejection under 35 U.S.C. § 112, First paragraph; Written Description

The Examiner rejected claims 14-27 for failing to comply with the written description requirement. The applicants respectfully traverse this rejection.

Without acquiescing to the rejection, claim 14 now refers to "bovine" in place of "cattle." This should render this rejection moot with respect to the word "cattle."

Further, applicant's cancellation of claim 16 renders this rejection moot with respect to claim 16.

Claim 17 now specifies "mouse, pig, or a bovine."

The detailed explanation presented above regarding the new matter issue should also further address this rejection for lack of written description. It is evident that there is high degree of sequence identity, structure/function relationship, and predictability of the specified domains. Thus, the withdrawal of this rejection is respectfully requested

D. Rejection under 35 U.S.C. § 112, First paragraph; Enablement

Claims 14-27 stand rejected as failing to comply with the enablement requirements. The applicants respectfully traverse this rejection.

As noted above, the term "bovine" is now used in place of "cattle."

Without acquiescing to the rejection, the terms "targeting sequences" and "targeted location by homologous recombination" are removed from claim 14 without prejudice to the scope of the claims. Such language is not needed to define the invention as claimed, and the remaining language of the claim now stands alone without this language. Thus, this rejection should be rendered moot.

Page 7 of the office action alleges that the specification is limited in that only mice were exemplified and that resistance to BHV-1 virus was not demonstrated. The previously presented pig data is also questioned.

Attached hereto is a declaration by Dr. Pierre Cherel, which shows that by following the techniques of the subject application/specification, methods of the subject invention were successfully used to produce pigs that are resistant to infection by a PRV virus.

Briefly, the data shows a comparison of mortality rate between two separate lines of transgenic pigs expressing the fusion protein of the current invention and the control pigs. The data shows that at 20 days post-infection, pigs from two transgenic lines exhibited only about 10% and 50% mortality rates when infected with the PRV virus. Control pigs on the other hand exhibited a 100% mortality rate when infected with the PRV virus.

The data therefore provides *in vivo* demonstration regarding efficacy of methods described in the instant application to produce transgenic pigs expressing fusion proteins of the current invention that exhibit resistance to infection by PRV viruses.

The subject application shows that the claimed methods can be applied to the specified animals. The techniques were applied with success - without the perceived problems discussed in the office action.

In addition, US Patent No. 5,633,076 (1997; DeBoer *et al.*), for example, discloses a method of producing a transgenic bovine by pronuclear injection technique. The issue date of this issue patent is prior to the filing date of the subject application, and therefore, it was within the abilities of a skilled artisan to produce a transgenic bovine. This should help to show that subject teachings can be applied with success to all of the specified animals, and that the skilled artisan can practice the full scope the claimed subject matter.

Regarding enablement for BHV-1, the application also contains sections documenting *in vitro* results for BHV-1 resistance on transformed cell lines, which show that methods of the subject invention extend to BHV-1 virus. *See e.g.* Table 9, paragraph 173, page 10 of the published application.

Regarding the statements in the office action alleging variable outcomes from microinjection procedures, Dr. Cherel adds in his attached expert declaration that any perceived issues regarding such variability, generated by position effects resulting from random insertion of the transgene, did not affect the efficiency of the subject methods. The subject methods were used to generate both murine and porcine transgenic lines, thus showing repeatable and effective resistance to *in vivo* viral challenges. The presently claimed methods were thus shown to be repeatable, effective, and efficient.

In light of all the foregoing, the applicants respectfully request withdrawal of rejections under 35 U.S.C. § 112, first paragraph.

E. Rejection under 35 U.S.C. § 103; non-obviousness

Claims 14, 15, 17, 18, 20, 23 and 25-27 stand rejected as being obvious over Fiume et al. (U.S. Patent No. 6,469,155) in view of Bujard et al. (U.S. Patent No. 5,866,755). The applicants respectfully traverse this rejection.

First, Bujard does not appear to be otherwise mentioned in the office action. Bujard is entitled, "Animals transgenic for a tetracycline-regulated transcriptional inhibitor" and does not appear to be cited for particular relevance.

Claim 14 of the subject application specifies introducing, into the specified animal, a transgene including a coding sequence for a fusion protein of a V domain or VCC domain of porcine or bovine nectin 1 (a receptor protein), and an Fc fragment of a specified immunoglobulin.

Fiume does not teach, suggest, or otherwise show or make obvious transgenic mice containing a transgene encoding the specified fusion protein.

The applicants understand that Fiume might relate to more than one single concept, but combining these teachings would not lead the skilled artisan to what is now claimed. It is important to understand these distinctions.

Fiume relates primarily to the identification of a receptor that binds (glycoprotein D of) herpes virus. This is the title of that patent.

Fiume teaches a transgenic mouse that produces the full-length, functional, transmembrane receptor for herpes virus, which renders the mice hyper-sensitive to infection by herpesvirus. Fiume uses this mouse to screen for preventative and therapeutic agents that block binding of the herpes virus to that functional transmembrane receptor and that thereby prevent infection by the virus.

Fiume teaches preventatives and therapies for herpes, but these are in the form of antibodies and the like that bind and block the cell-bound (full-length, functional) receptor.

Fiume also constructed fusion proteins comprising segments of the extracellular portion of the receptor to identify specific binding domains. This was done so those domains could be specifically targeted for blockage by antibodies in an attempt to prevent binding.

Unlike Fiume, the subject fusion proteins produced by animals are soluble and non-membrane bound. According to embodiments of the subject invention, soluble fusion proteins are produced by the animal in excess so that herpes virus bind those fusion proteins to dilute the virus and its ability to cause illness in the mammal. In contrast, the whole point of Fiume was to obtain medicaments that block binding.

The efficacy of the subject approach was not even contemplated or predictable in light of Fiume. The effect of presence of excess, soluble fusion protein, produced by and present in the animal, could not have been predicted, even *assuming* in hindsight that there was a suggestion to do so (which there was not). Fiume does not contemplate such arrangements, and there was no reason for Fiume to do so. The subject application shows surprising success using this much different approach.

Even assuming that there was a suggestion to do so (which there was not), Fiume does not at all address what might have happened had the fusion proteins been produced by the mice. In order for Fiume to assess blocking ability of an antibody, for example, and the subsequent ability of a virus to bind the receptor and infect the cells, one needed functional, transmembrane / membrane-bound receptors, such as those of Fiume. Thus, modifying the teachings of Fiume, as suggested in the office action, so that a transgenic mouse *would* produce such protein would destroy the operability of Fiume. Such a reconstruction of the art is impermissible under *In re Sponnoble*, 405 F.2d 578 (CCPA 1969). Unlike the full-length / transmembrane receptor protein, the fusion protein of the V or the VCC domain of the receptor protein and the Fc fragment of IgG is a soluble, non-membrane protein.

As Dr. Cherel adds in his attached expert declaration, Fiume relates to a receptor identification process, which stands alone as a generic tool. Fiume involved making cell lines (not whole animals), and testing expression of a library of proteins in those cells. This was done to infer from that the potential role of receptors. Fiume also provides a generic tool and making cells "resistant" to a virus (essentially by a selection process under viral pressure) to check to see which potential treatments could block the animal's sensitivity to virus. If Fiume mentions some "cells made resistant," that might be true only with respect to the "receptor discovery tool." Fiume does not teach or suggest a transgene / transgenic mammal approach for doing so, as

taught by the subject application. Even where soluble proteins are considered by Fiume for their virus binding properties as such, it is only in the context of a medicament definition, and never within the context of a transgenic rodent, which would have no value as a model for therapeutics testing.

The applicants understand that Fiume teaches some fusion proteins. However, the Fiume fusion proteins are not produced by a transgenic mouse. The fusions of Fiume were produced by and purified from the cell cultures and used in binding studies. Then, antibodies and the like were assessed for their ability to block virus binding to the binding domains. There was no reason provided by Fiume, or the art at that time, to go through all of the work for producing the fusions in whole mammals. While Fiume might suggest cells that could be used in binding-blocking studies, those cells are believed to produce the medicament or *the blockers* (e.g., antibodies), which thereby render the cells "resistant" so to speak.

As stated by Dr. Cherel in his attached declaration, the soluble fusion proteins of Fiume are used by Fiume to define targets for antibodies and also for discovery of antiviral compounds (by binding to viral particles) as such. One main difference between the soluble proteins of the subject application and Fiume is that Fiume relates to drugs / drug discovery, while the subject application surprisingly shows (see the enablement rejections regarding unpredictability!) that transgenic mammals expressing the specified fusion genes are unexpectedly resistant because of the fusion protein production. This was in no way taught, suggested, or predictable in light of Fiume.

The transgenic mice of Fiume, which again expressed full-length, membrane-bound, functional receptors, were used to assess the ability of novel antibodies and the like to block and prevent viral binding and infection. The approach used by Fiume was to use a third component (e.g., and antibody) to block attachment of the virus to the full-length, functional receptor. The transgenic mice of Fiume were suited for that purpose – to test efficacy of third component blockage.

In contrast, the subject invention provides a surprising new approach – to provide binding domains systemically in excess directly by the animal. This was a new approach not even

contemplated by Fiume or the art at that time, and the success could not have been predicted based on Fiume and the art at the time of Fiume.

In light of the foregoing, it should be clear that the examiner has not set forth even a *prima facie* case for obviousness of a transgenic mouse rendered resistant to infection, wherein the mouse contains a transgene encoding a chimeric fusion protein.

In light of the foregoing, the applicants respectfully request withdrawal of the obviousness rejection.

Conclusion

The subject application is believed to be in condition for allowance, and such action is respectfully requested.

The Assistant Commissioner is hereby authorized to charge any fees under 37 CFR §1.17 as required by this paper to Deposit Account 02-0390.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Jay M. Sanders
Patent Attorney
Registration No. 39,355
Phone No.: 317 237 1245
Fax No.: 317 237 1000
Address: 300 N. Meridian Street
Suite 2700
Indianapolis, IN 46204

JMS/jlk
Attachments: Petition and Fee For Extension of Time Under 37 CFR §1.136(a)
Dr. Pierre Cherel's Declaration
Sequence alignment between the V and VCC domain of the porcine and bovine HveC protein
Milne *et al.* reference